Remarks/Arguments

A. Claim Amendments

Claims 7, 15 and 16 have been amended. Claim 8 has been cancelled.

Support for the amendment to claim 7 can be found in claim 8 as originally filed. Support for the amendment to claim 15 can be found, for example, on p4, lines 9-15 and p6, lines 4-11. Support for the amendment to claim 16 can be found, for example, on p4, lines 9-15.

This Amendment adds no new matter.

B. Rejection of claims 7, 15, 18 and 19 under 35 U.S.C. 102(b)

Claims 7, 15, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Langer et al. The Examiner asserts that Langer et al. teaches a method of making a semi-interpenetrating network comprising crosslinked chitosans and hyaluronic acid (Office Action, p2). The Examiner contends that since the ionic compound is not crosslinked, the reaction conditions would "inherently be such that the amine groups would not be protonated, and the hydroxyl groups are not reacted, as these would result in crosslinking of hyaluronic acid" (p4).

Langer et al. does not anticipate the present claims because Langer et al. does not teach each and every limitation of the claims, either expressly or inherently, and because Langer et al. does not enable the claimed method. Firstly, Langer et al. does not disclose that the cross-linking reaction is conducted at a pH between about 7 and about 8, that the amine groups are not protonated and that the crosslinked gel is prepared from a "water-soluble derivative of a basic polysaccharide." The Examiner contends that these elements of the invention are inherent in Langer's teaching. The Examiner is incorrect. Chitosan and hydrogels of chitosan are not soluble at neutral pH or mildly alkaline pH as would be required for the cross-linking reaction to be conducted at pH between 7 and 8. Chitosan and hydrogels thereof are soluble only in *acidic* aqueous solutions. Applicant's disclosure teaches that chitosan is only soluble in "aqueous solutions only when protonated with acids" (p5, line 27). In further support of this fact, the Examiner's attention is directed to the following references (including Hudson et al., cited in the Office Action):

Hudson et al. discloses that although chitin is insoluble in many common solvents, chitosan "dissolves in many common aqueous acidic solutions" (p2) and "is soluble in aqueous acidic solution existing as a randomly coiled cationic polyelectrolyte" (p5).

Kumar et al. discloses that chitosan's "rich amine functionality confers water solubility at low pH. At higher pH's (greater than 6.5), the amines are deprotonated and chitosan is insoluble" (abstract).

Len-Gibson et al. describes the preparation of a water soluble diisocyanate useful as a cross-linking agent for generating chitosan gel formations which are "typically hindered by solubility issues." Len-Gibson et al. further teaches that the cross-linking reaction using diisocyanate was conducted under acidic conditions (p200, last paragraph).

Therefore, contrary to the Examiner's contention, Langer et al. does not inherently disclose the reaction conditions required by the present claims. The present claims firstly require the hydrogel be formed from a "water-soluble derivative of a basic polysaccharide." Chitosan is a basic polysaccharide but, as discussed above, is not soluble in water. Chitosan and hydrogels thereof would not be soluble at a pH between about 7 and about 8 as required by the present claims. Chitosan becomes soluble only in aqueous acidic solutions. Furthermore, the amine groups of chitosan would be protonated in aqueous acidic solution and the claim language expressly requires that the reaction avoids protonation of the amine groups.

In addition, Langer et al. does not enable the present invention. In order to anticipate an invention, the prior art must enable one of ordinary skill in the art to make the invention *without undue experimentation* (Impax Labs. Inc. v. Aventis Pharm.Inc., 468 F.3d 1366, 1383, 81 USPQ2d 1001, 1013 (Fed. Cir. 2006)). Some of the facts used to determine whether experimentation is undue are: the quantity of experimentation required, the amount of direction or guidance present in the prior art, the presence and absence of working examples in the prior art, the nature of the invention, and the breadth of the claims (In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); Impax Labs. Inc. v. Aventis Pharm. Inc.).

The invention is directed to an improved method of preparing semi-interpenetrating networks comprising a crosslinked water-soluble derivative of a basic polysaccharide and a non-crosslinked anionic polysaccharide. The invention requires that the crosslinking reaction be conducted under conditions that avoid protonation of the amine groups of the basic

polysaccharide and avoid reaction of the functional groups of the anionic polysaccharide. Claim 7 has been amended to expressly recite that the cross-linking reaction is conducted at neutral or mildly alkaline pH.

Langer et al. is directed to preparing polymeric interpenetrating and semi-interpenetrating network compostions upon exposure to "active species" (Column 2, lines 19-25). Langer et al. describes "active species" as free radicals, cations and anions (Column 7, lines 11-12). The description with respect to chitosan is exceedingly limited. Langer et al. simply discloses that chitosan can be cross-linked with a water soluble diisothiocyanate which will react with the amines to form a crosslinked gel (Column 6, lines 45-54). Langer et al. does not disclose conducting the crosslinking reaction of chitosan at neutral or mildly alkaline pH. As discussed above, chitosan is insoluble at these pHs. Langer et al. provides no guidance as to how chitosan can be crosslinked under the recited reaction conditions. There is not a single working example directed to crosslinking chitosan or a derivative thereof, much less to crosslinking chitosan under the recited reaction conditions.

Furthermore, Langer et al. does not disclose that a water-soluble derivative of chitosan is part of semi-interpenetrating network which also comprises an anionic polysaccharide which is not crosslinked. In the Office Action, the Examiner points to the portion of Langer et al. which pertains hyaluronic acid used to form an injectable gel (Column 4, lines 50+) and to general language to the advantages of semi-interpenetrating networks where the exemplified network is of PEO and demethacrylated PEO (Column 10, lines 9+). Langer et al. does not provide any description, guidance or working example wherein a semi-interpenetrating network comprises crosslinked chitosan and non-crosslinked hyaluronic acid. Langer et al.'s teaching with respect to hyaluronic acid is limited to its use as a gel (therefore, it is crosslinked). A semi-interpenetrating network having all of the claimed elements and a method of preparing the claimed network is not explicitly or inherently described by Langer et al.

Based on the lack of specific teaching directed to the claimed semi-interpenetrating network and the lack of teaching with respect to the reaction conditions required to form said network, one of ordinary skill in the art reviewing Langer et al. would have had to pick and choose among the multitude of crosslinking polymers described in Langer et al. and somehow arrive at those required by the present claims. There is nothing in Langer et al. that

would lead one of skill in the art to choose a water-soluble derivative of a basic polysaccharide which possesses amine groups as the crosslinking component *and* an anionic polysaccharide as the non-crosslinking component. Furthermore, there is no teaching in Langer et al. that would lead one of skill in the art to devise the claimed reaction conditions in order to prepare the claimed semi-interpenetrating network. Langer et al.'s teaching to semi-interpenetrating networks is general at best and the amount and level of experimentation required to arrive at the claimed method would far exceed the threshold of undue experimentation.

Because Langer et al. neither enables the claimed method nor inherently or expressly discloses the limitations required by the present claims, Langer et al. does not anticipate the claimed invention. Withdrawal of this rejection is therefore respectfully requested.

C. Rejection of claims 8, 9, 16 and 17 under 35 U.S.C. 103(a)

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Langer et al. The Examiner states that although Langer et al. does not teach the claimed pH, Langer et al. does teach that pH affects the degree of crosslinking of ionically crosslinkable polymers and it would have been obvious to have optimized the pH and the motivation would have been to "reduce crosslinking of the ionic component." Claims 16-17 are rejected under 35 U.S.C. 103(a) as unpatentable over Langer et al. in view of Hudson et al. The Examiner states that Langer et al. does not teach the use of a claimed chitosan derivative. The Examiner alleges that Hudson et al. teaches the use of partially N-acetylated chitosan "in a cross-linked chitosan gel" (Office Action, p4). The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the acetylated chitosan taught by Hudson "in the composition of Langer et al., and the motivation to do so would have been…this chitosan is soluble at neutral conditions, removing the need for a neutralization step" (Office Action, p4).

With regard to claims 8-9, Langer et al. would not render the claimed method of preparing a semi-interpenetrating network obvious. The Examiner's rejection is based on the premise that it would be obvious to optimize the pH used for crosslinking. The Examiner states that the motivation to "optimize pH" would have been "as Langer et al. suggests, to reduce the crosslinking of the ionic component (1:l27-29)" (Office Action, p3). The section

of Langer et al. referred to by the Examiner does not disclose using pH to *reduce* crosslinking of an ionic polysaccharide, but rather, how the specific polymers described in WO 94/25080 "…crosslink ionically, as a function of ionic strength, temperature, pH or combinations thereof" (Column 1, lines 27-29). WO 94/25080, in turn, is directed to the use of polymerizing hydrogels for injection. The disclosure of WO94/25080 is directed mainly to the use of alginate polymers but provides examples of other polymeric materials, such as hyaluronic acid, that can be used to form injectable hydrogels (p15, line 36). WO94/25080 is directed to the preparation of hydrogels using the disclosed polymer materials not to semi-interpenetrating networks where an anionic polysaccharide is *not* cross-linked. Far from teaching that the polymeric materials can avoid cross-linking at neutral or mildly alkaline pH as required for hyaluronic acid used according to the present claims, WO94/25080 teaches that crosslinking is carried out at physiologic pH (p20, line 26-29) and more specifically, at pH 7.4 (p25, line 7; p27, line 32). Therefore, Langer et al. does not provide the motivation to use neutral or mildly alkaline pH to prepare a semi-interpenentrating network as required by the present claims.

With regard to claims 16-17, the Examiner rejects these claims over Langer et al. in view of Hudson et al. The deficiencies of Langer et al. have been described in detail above. The disclosure of Hudson et al. does not add to the teaching of Langer et al. to render the instant claims obvious. The Examiner's characterization of Hudson et al. is more detailed than the actual teaching. With respect to the use of N-acetylated chitosan having a degree of acetylation from 45-55%, the Examiner points to page 2 of Hudson et al. as teaching this specific chitosan derivative. This specified section of Hudson et al. is in fact directed to the deacetylation of chitin to chitosan by the enzyme chitin deacetylase and provides no disclosure of N-accytated chitosan having 45-55% acetylation. There is no disclosure in Hudson et al. related to N-acetylated chitosan with a 45-55% acetylation. In addition, the Examiner points to page 8 of Hudson et al. as teaching use of N-acetylated chitosan with the specified degree of acetylation in a crosslinked gel (Office Action, p4). The indicated portion of Hudson et al. simply states that "Cross-linked chitosan has potential in tablet form because of its low solubility in the stomach." There is nothing in Hudson et al. that discloses a gel of crosslinked chitosan derivative, much less a semi-interpenetrating network comprising the claimed derivative.

The Examiner states that it would have been obvious to use the partially acetylated chitosan taught by Hudson et al. in the composition of Langer et al. because this partially acetylated chitosan is soluble in neutral pH and a neutralization step would be avoided. However, as discussed above, Langer et al. does not disclose a method of preparing a semi-interpenetrating network comprising the specific crosslinked water-soluble derivatives of chitosan required by claims 16-17 and non-crosslinked anionic polysaccharide. Hudson does not describe the use of water-soluble derivatives of chitosan or other basic polysaccharides in a semi-interpenetrating network. Neither Langer et al. nor Hudson et al. teach reaction conditions that permit crosslinking of the water-soluble derivative of a basic polysaccharide while avoiding protonation of the amine groups of the basic polysaccharide and avoid reaction of the functional group on the anionic polysaccharide. One of ordinary skill in the art combining the teachings of Langer et al. with Hudson et al. would simply not have arrived at the claimed invention.

In view of the arguments presented above, Langer et al. alone or in combination with Hudson et al. does not obviate the present claims. Withdrawal of this rejection is therefore respectfully requested.

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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